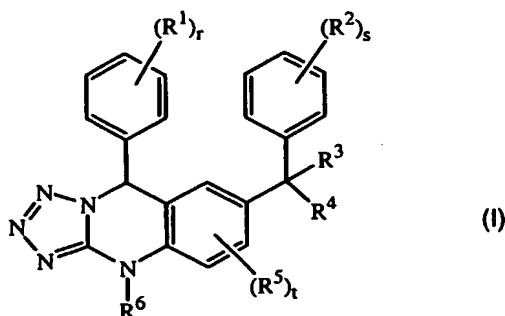


Claims

A compound of formula (I):



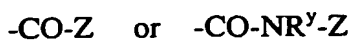
or a pharmaceutically acceptable salt or N-oxide or stereochemically isomeric form thereof, wherein

r and s are each independently 0, 1, 2 or 3;

t is 0, 1, or 2;

each R¹ and R² are independently hydroxy, halo, cyano, nitro, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p, -C₃₋₁₀cycloalkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, R²⁰SC₁₋₆alkyl, trihalomethyl, arylC₁₋₆alkyl, Het¹C₁₋₆alkyl, -C₁₋₆alkyl-NR¹⁸R¹⁹, -C₁₋₆alkylNR¹⁸C₁₋₆alkyl-NR¹⁸R¹⁹, -C₁₋₆alkylNR¹⁸COC₁₋₆alkyl, -C₁₋₆alkylNR¹⁸COAlkAr¹, -C₁₋₆alkylNR¹⁸COAr¹, C₁₋₆alkylsulphonylaminoC₁₋₆alkyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, -OC₁₋₆alkyl-NR¹⁸R¹⁹, trihalomethoxy, arylC₁₋₆alkyloxy, Het¹C₁₋₆alkyloxy, C₂₋₆alkenyl, cyanoC₂₋₆alkenyl, -C₂₋₆alkenyl-NR¹⁸R¹⁹, hydroxycarbonylC₂₋₆alkenyl, C₁₋₆alkyloxycarbonylC₂₋₆alkenyl, C₂₋₆alkynyl, -CHO, C₁₋₆alkylcarbonyl, hydroxyC₁₋₆alkylcarbonyl, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, -CONR¹⁸R¹⁹, -CONR¹⁸-C₁₋₆alkyl-NR¹⁸R¹⁹, -CONR¹⁸-C₁₋₆alkyl-Het¹, -CONR¹⁸-C₁₋₆alkyl-Ar¹, -CONR¹⁸-O-C₁₋₆alkyl, -CONR¹⁸-C₁₋₆alkenyl, -NR¹⁸R¹⁹, -OC(O)R²⁰, -CR²⁰=NR²¹, -CR²⁰=N-OR²¹, -NR²⁰C(O)NR¹⁸R¹⁹, -NR²⁰SO₂R²¹, -NR²⁰C(O)R²¹, -S-R²⁰, -S(O)-R²⁰, -S(O)₂R²⁰, -SO₂NR²⁰R²¹, -C(NR²²R²³)=NR²⁴,

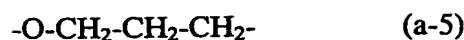
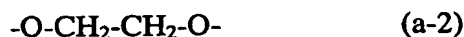
or a group of formula



in which R^y is hydrogen or C₁₋₄alkyl and Z is phenyl or a 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, sulphur and nitrogen, the phenyl or heterocyclic

ring being optionally substituted by one or two substituents each independently selected from halo, cyano, hydroxycarbonyl, aminocarbonyl, C₁₋₆alkylthio, hydroxy, -NR¹⁸R¹⁹, C₁₋₆alkylsulphonylamino, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyloxy or phenyl; or

two R¹ and R² substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula



R¹⁶ and R¹⁷ are independently hydrogen or C₁₋₆ alkyl;

R¹⁸ and R¹⁹ are independently hydrogen, C₁₋₆ alkyl or

-(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, or together with the adjacent nitrogen atom form a 5- or 6-membered heterocyclic ring optionally containing one, two or three further heteroatoms selected from oxygen, nitrogen or sulphur and optionally substituted by one or two substituents each independently selected from halo,

hydroxy, cyano, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyloxy, OCF₃,

hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl,

mono- or di-(C₁₋₆alkyl)aminocarbonyl, amino, mono- or di-(C₁₋₆alkyl)amino,

C₁₋₆alkylsulfonylamino, oxime, or phenyl;

R²⁰ and R²¹ are independently hydrogen, C₁₋₆alkyl,

-(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl or arylC₁₋₆alkyl;

R²², R²³ and R²⁴ are independently hydrogen and C₁₋₆alkyl or C(O) C₁₋₆alkyl;

p is 0 or 1;

R³ is hydrogen, halo, cyano, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, haloC₁₋₆alkyl,

cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, arylC₁₋₆alkyloxy

C₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonyl

C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, -C₁₋₆alkyl-NR¹⁸R¹⁹,

-C₁₋₆alkyl-CONR¹⁸R¹⁹, arylC₁₋₆alkyl, Het¹C₁₋₆alkyl,

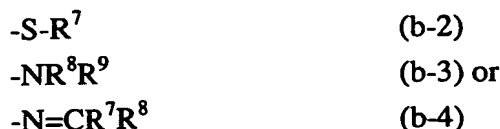
C₂₋₆alkenyl, -C₂₋₆alkenyl NR¹⁸R¹⁹, C₂₋₆alkynyl,

hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, aryl, or Het¹; or

a radical of formula

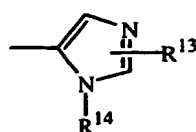


(b-1)



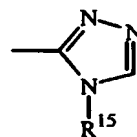
- 5 wherein R^7 is hydrogen, C_{1-6} alkyl, $-(CR^{16}R^{17})_p-C_{3-10}$ cycloalkyl, aryl C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylcarbonyl or $-C_{1-6}$ alkylC(O)OC C_{1-6} alkyl $NR^{18}R^{19}$, or a radical of formula $-Alk-OR^{10}$ or $-Alk-NR^{11}R^{12}$;
- 10 R^8 is hydrogen, C_{1-6} alkyl, $-(CR^{16}R^{17})_p-C_{3-10}$ cycloalkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;
- R^9 is hydrogen, hydroxy, C_{1-6} alkyl, $-(CR^{16}R^{17})_p-C_{3-10}$ cycloalkyl, C_{1-6} alkylcarbonyl C_{1-6} alkyl, aryl C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyloxy, a group of formula $-NR^{18}R^{19}$, C_{1-6} alkylcarbonylamino, C_{1-6} alkylcarbonyl, halo C_{1-6} alkylcarbonyl, aryl C_{1-6} alkylcarbonyl,
- 15 arylcarbonyl, C_{1-6} alkyloxycarbonyl, trihalo C_{1-6} alkyloxycarbonyl, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, aminocarbonyl, mono- or di(C_{1-6} alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl and C_{1-6} alkyloxycarbonyl substituents, aminocarbonylcarbonyl,
- 20 mono- or di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonyl, or a radical of formula $-Alk-OR^{10}$ or $Alk-NR^{11}R^{12}$;
- wherein Alk is C_{1-6} alkanediyl;
- R^{10} is hydrogen, C_{1-6} alkyl, $-(CR^{16}R^{17})_p-C_{3-10}$ cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylcarbonyl or hydroxy C_{1-6} alkyl;
- 25 R^{11} is hydrogen, C_{1-6} alkyl, $-(CR^{16}R^{17})_p-C_{3-10}$ cycloalkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;
- R^{12} is hydrogen, C_{1-6} alkyl, $-(CR^{16}R^{17})_p-C_{3-10}$ cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} alkylcarbonyl;

30 R^4 is a radical of formula



(c-1)

or



(c-2)

wherein R^{13} is hydrogen, halo or C_{1-6} alkyl;

R^{14} is hydrogen or C_{1-6} alkyl;

R^{15} is hydrogen or C_{1-6} alkyl;

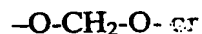
R⁵ is cyano, hydroxy, halo, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, or a group of formula -NR¹⁸R¹⁹ or -CONR¹⁸R¹⁹;

5

R⁶ is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, cyanoC₁₋₆alkyl, -C₁₋₆alkylCO₂R²⁰, aminocarbonylC₁₋₆alkyl, -C₁₋₆alkyl-NR¹⁸R¹⁹, R²⁰SO₂, R²⁰SO₂C₁₋₆alkyl, -C₁₋₆alkyl-OR²⁰, -C₁₋₆alkyl-SR²⁰, -C₁₋₆alkylCONR¹⁸-C₁₋₆alkyl-NR¹⁸R¹⁹, -C₁₋₆alkylCONR¹⁸-C₁₋₆alkyl-Het¹,
 10 -C₁₋₆alkylCONR¹⁸-C₁₋₆alkyl-Ar¹, -C₁₋₆alkylCONR¹⁸-Het¹,
 -C₁₋₆alkylCONR¹⁸Ar¹, -C₁₋₆alkylCONR¹⁸-O-C₁₋₆alkyl,
 -C₁₋₆alkylCONR¹⁸-C₁₋₆alkenyl, -Alk-Ar¹ or -AlkHet¹;

15

Ar¹ is phenyl, naphthyl or phenyl or naphthyl substituted by one to five substituents each independently selected from halo, hydroxy, cyano, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, -alkylNR¹⁸R¹⁹, C₁₋₆alkyloxy, OCF₃, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, -CONR¹⁸R¹⁹, -NR¹⁸R¹⁹, C₁₋₆alkylsulfonylamino, oxime, phenyl, or a bivalent substituent of formula



20

Het¹ is a mono- or bi-cyclic heterocyclic ring containing one or more heteroatoms selected from oxygen, sulphur and nitrogen and optionally substituted by one or two substituents each independently selected from halo, hydroxy, cyano, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, -alkylNR¹⁸R¹⁹, C₁₋₆alkyloxy, OCF₃, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl,
 25 -CONR¹⁸R¹⁹, -NR¹⁸R¹⁹, C₁₋₆alkylsulfonylamino, oxime or phenyl.

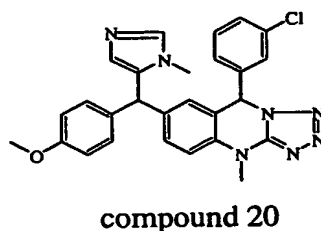
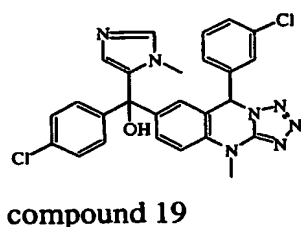
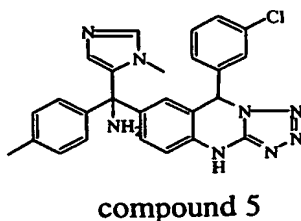
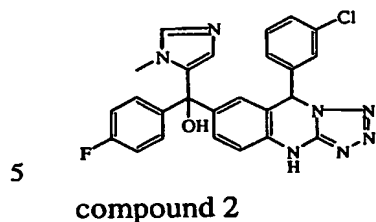
30

2. A compound according to claim 1 wherein r is 1, s is 1 and t is 0; R¹ is halo; R² is halo, C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkyloxycarbonyl; R³ is hydrogen or a radical of formula (b-1) or (b-3) wherein R⁷ is hydrogen or C₁₋₆alkyl, R⁸ is hydrogen and R⁹ is hydrogen; R⁴ is a radical of formula (c-1) or (c-2) wherein R¹³ is hydrogen, R¹⁴ is C₁₋₆alkyl and R¹⁵ is C₁₋₆alkyl; and R⁶ is hydrogen, C₁₋₆alkyl, -(CH₂)_p-C₃₋₁₀cycloalkyl, -C₁₋₆alkylCO₂C₁₋₆alkyl or -Alk-Ar¹.

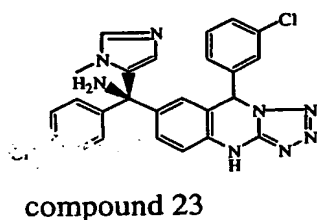
35

3. A compound according to claim 1 and 2 wherein r is 1, s is 1 and t is 0; R¹ is halo; R² is halo, C₁₋₆alkyl or C₁₋₆alkyloxy; R³ is hydrogen, hydroxy or amino; R⁴ is a radical of formula (c-1) wherein R¹³ is hydrogen and R¹⁴ is C₁₋₆alkyl; and R⁶ is hydrogen or C₁₋₆alkyl.

4. A compound according to claim 1, 2 and 3 selected from compounds No 2, No 5, No 19, No 20 and No 23.

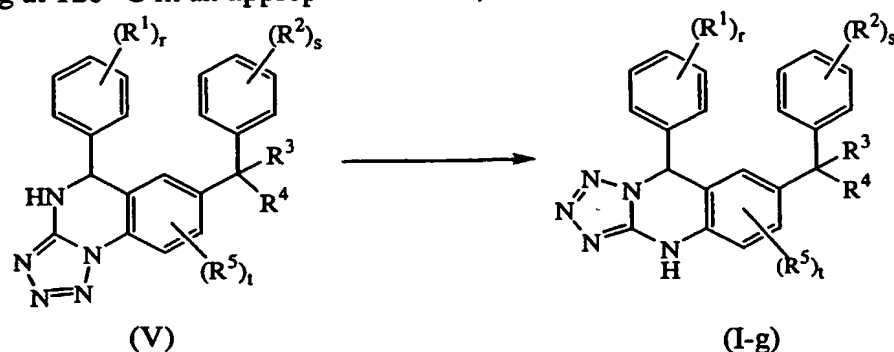


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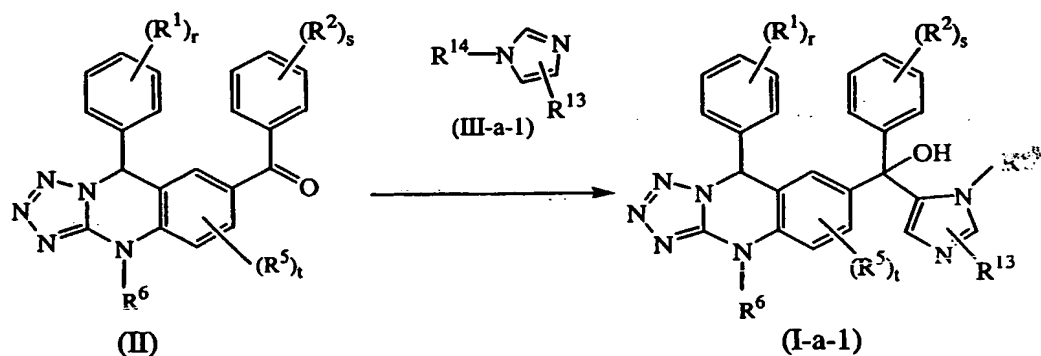


5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier,
15 and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 4.
6. A process for preparing a pharmaceutical composition as claimed in claim 5 wherein
20 a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.
7. A compound according to any of claims 1 to 4 for use as a medicine.
8. The use of a compound according to claim 1 to 4 in the manufacture of a
25 medicament for inhibiting tumor growth.
9. The use of a compound according to claim 1 to 4 in the manufacture of a medicament to treat proliferative disorders.
- 30 10. A process for the preparation of a compound as claimed in claim 1 which comprises:

a) Converting intermediates of formula (V) in compounds of formula (I) wherein R^6 is hydrogen said compounds being referred to as compounds of formula (I-g) by heating at 120 °C in an appropriate solvent; and



5 b) reacting an intermediate ketone of formula (II) with an intermediate imidazole of formula (III-a-1) wherein R^{14} is C_{1-6} alkyl with the formation of compounds of formula (I) wherein R^4 represents a radical of formula (c-1), R^3 is hydroxy and R^{14} is C_{1-6} alkyl, said compounds being referred to as compounds of formula (I-a-1); and

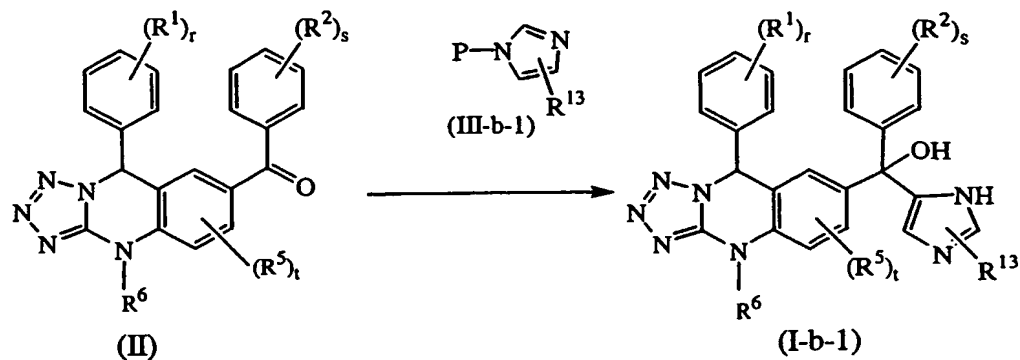


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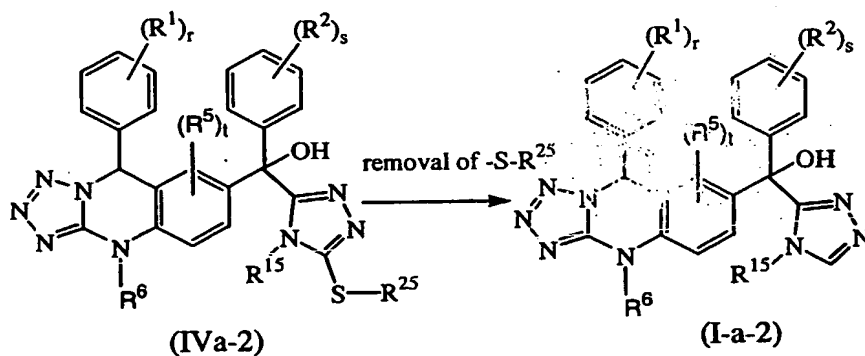
c) reacting an intermediate ketone of formula (II) with an intermediate imidazole reagent of formula (III-b-1) wherein P is an optional protective group and R^{14} is hydrogen and subsequently removal of P with the formation of a compound of formula (I) wherein R^4 is a radical of formula (c-1), R^3 is hydroxy and R^{14} is hydrogen said compound being referred to as compounds of formula (I-b-1); and

15

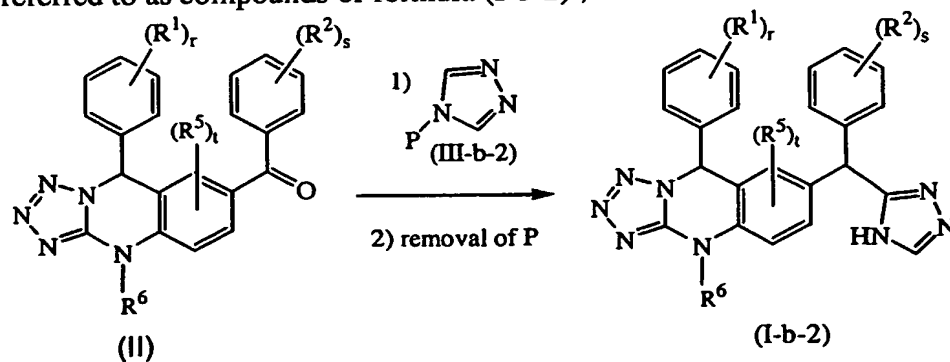
-55-



- d) removing the $-S-R^{25}$ group, wherein R^{25} is hydrogen or C_{1-6} alkyl from the intermediate of formulae (IVa-2) wherein R^4 is a radical of formula (c-2), R^{15} is C_{1-6} alkyl and R^3 is hydroxy with the formation of compounds of formula (I), wherein R^4 is a radical of formula (c-2), R^{15} is C_{1-6} alkyl and R^3 is hydroxy, said compounds being referred to as compounds of formula (I-a-2); and



- e) reacting an intermediate ketone of formula (II) with an intermediate triazole reagent of formula (III-b-2) wherein P is an optional protective group and subsequently removal of P with the formation of a compound of formula (I) wherein R^4 is a radical of formula (c-2), R^3 is hydroxy and R^{14} is hydrogen said compound being referred to as compounds of formula (I-b-2) ; and



f) optionally effecting one or more of the following conversions in any desired order:

(i) converting a compound of formula (I) into a different compound of formula (I);

(ii) converting a compound of formula (I) into a pharmaceutically acceptable salt or
5 N-oxide thereof;

(iii) converting a pharmaceutically acceptable salt or N-oxide of a compound of formula (I) into the parent compound of formula (I);

(iv) preparing a stereochemical isomeric form of a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof.